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OF BLOOD

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ADRENALIN INJECTIONS

BY W. B. CANNON AND HORACE GRAY

[FROM THE LABORATORY OF PHYSIOLOGY IN THE HARVARD MEDICAL SCHOOL]

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[From the Laboratory of Physiology in the Harvard Medical School]

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IN 1903, while tracing in dogs the course of adrenalin hyperglycaemia, Vosburgh and Richards first noted that simultaneously with the increase of blood sugar there occurred more rapid coagulation of the blood. In some cases the diminution was as much as four-fifths the coagulation time of the control. Since this result was obtained by painting adrenalin on the pancreas, as well as by intraperitoneal injection, they concluded that "the phenomenon appears to be due to the application of adrenalin to the pancreas."¹ Six years later during a study of the effect of adrenalin on internal hemorrhage, Wiggers examined incidentally the evidence presented by Vosburgh and Richards, and after many tests on five dogs found "never the slightest indication that adrenalin, either when injected or added to the blood, appreciably hastened the coagulation process."² In 1911, von den Velden reported that adrenalin (about 0.007 mg. per kilo) decreased the coagulation time in man about one-half — an effect appearing 11 minutes after administration by mouth, and 85 minutes after subcutaneous injection. He affirmed also, but without describing the conditions or giving figures, that adrenalin decreases coagulation time in vitro. He did not attribute the coagulative effect of adrenalin in patients to this direct action on the blood, however, but to vasoconstriction disturbing the normal circulation and

¹ VOSBURGH and RICHARDS: This journal, 1903, ix, p. 39.

² WIGGERS: Archives of internal medicine, 1909, iii, p. 152.

thereby the normal equilibrium between blood and tissue. In consequence, the tissue juices with their coagulative properties enter the blood, so he assumes. In support of this theory he offers his observation that coagulation time is decreased after the nasal mucosa has been rendered anemic by adrenalin pledgets.¹ Von den Velden's claim for adrenalin given by mouth was subjected to a single test on man by Dale and Laidlaw, but their result was completely negative."²

The importance of Vosburgh and Richard's observation, the thoroughly discordant testimony of later investigators, as well as the meager and incidental nature of all the evidence that has been adduced either for or against the acceleration of clotting by adrenalin, made desirable a further study of this matter. In doing so we have employed cats as subjects. Usually they were quickly decerebrated under ether, and then continuance of the drug became unnecessary. Body temperature was maintained by means of an electric heating pad. Respiration proceeded normally except in a few instances (in which, presumably, there was hemorrhage into the medulla) when artificial respiration had to be given. The drawing of blood and the recording of coagulation were accomplished by methods already described.³ The adrenalin used was that prepared by Parke, Davis and Co.; it was injected either subcutaneously or intravenously.

The effects of subcutaneous injections. — The first observations were of this class.

Oct. 27. A cat weighing about 3 k. was given 3 c.c. adrenalin 1:1000, i.e., 1 mg. per kilo, under the skin. The animal, in this instance, was kept in uniform ether anaesthesia. Following is a record showing when blood was taken, and the coagulation time in each instance:

¹ VON DEN VELDEN: *Münchener medizinische Wochenschrift*, 1911, lviii, p. 187.

² DALE and LAIDLAW: *Journal of pathology and bacteriology*, 1912, xvi, p. 362.

³ CANNON and MENDENHALL: *This journal*, 1914, xxxiv, p. 225.

2.56 — Injection made	3.27 — 3.5 minutes
.59 — 6 minutes	.44 — 2 “
3.07 — 5.5 “	.55 — 2.5 “
.13 — 5 “	4.07 — 3 “
.20 — 6.5 “	.20 — 2 “
Average 5.7 minutes	2.6 minutes
4.44 — 6 minutes	
5.00 — 4.5 “	
5.50 — 5 “	
Average 5.2 minutes	

In this case the coagulation time remained at its usual level for about 20 minutes after the subcutaneous injection.¹ Thereafter for about an hour the coagulation time averaged 45 per cent of its previous duration. And widely separated tests made during the following hour indicated that approximately the initial rate of clotting had been regained.

The rather long period (nearly 30 minutes), in the case just cited, between the injection and the first appearance of rapid clotting was not the rule. As the following figures show, the coagulation time may become shortened quite promptly after subcutaneous injection, —

Oct. 29. 3.30 — 5.5 minutes	4.01 — 3.5 minutes
.36 — 5.5 “	.08 — 3.5 “
.44 — 3 c.c. adrenalin (1:1000) injected	.16 — 4.5 “
.46 — 5.5 minutes	.23 — 5 “
.53 — 4 “	.30 — 5.5 “

In this case nine minutes after the injection the change in the rate of clotting had begun, and it continued more rapid for the subsequent half-hour.

¹ This period is longer than is expected after the subcutaneous injection of any drug. As will be shown later, *strong* doses of adrenalin injected rapidly may not at first shorten the clotting process. Probably in some instances of subcutaneous injection of these strong doses, the drug enters the circulation more rapidly than in others and in consequence coagulation is not at first accelerated.

We did not attempt to find the minimal *subcutaneous* dose which would shorten clotting. A dose of 0.01 mg. per kilo, however, has proved effective, as shown by the following figures:

Feb. 3.	11.34	—	10	minutes	
	.45	—	9	“	
	.50 to .52	—	“		Adrenalin, 2.8 c.c., 1:100,000, injected under skin of groin in cat weighing 2.8 k.
	.55	—	10	minutes	
	12.06	—	7	“	
	.14	—	4	“	
	.19	—	5.5	“	
	.31	—	6	“	
	.37	—	7	“	
	.45	—	9	“	

As will be shown later, the dose in this instance was ten times the minimal effective *intravenous* dose. On the basis of these figures, less than a milligram of adrenalin given subcutaneously would be necessary to shorten clotting to a marked degree in a man of average weight (70 kg).

Not many observations were made by us on the effects of adrenalin administered subcutaneously. The amount of adrenalin reaching the vascular system and the rate of its entrance into the blood could be so much more accurately controlled by intravenous than by subcutaneous introduction that most of our attention was devoted to the latter method.

The effect of intravenous injections. — In this procedure a glass cannula was fastened in one of the external jugular veins, and filled with the same solution as that to be injected. A short rubber tube was attached and tightly clamped close to the glass. Later, for the injection, the syringe needle was inserted through the rubber and into the fluid in the cannula, the clip on the vein was removed, and the injection made.

The solutions employed intravenously were adrenalin 1:10,000, 1:50,000, and 1:100,000 in distilled water.

The smallest amount which produced any change in clotting time was 0.1 c.c. of 1:100,000, in a cat weighting 2 kg., a dose of 0.0005 mg. per kilo. Four tests previous to the injection averaged 5 minutes, and none was shorter than 4 minutes. Immediately after the injection the time was 2 minutes, but at the next test the effect had disappeared. Doubling the dose in the same cat — i.e., giving 0.2 c.c. (0.001 mg. per kilo) — shortened the coagulation time for about 40 minutes:

Dec. 23.	10.30 — 4 minutes	11.00 — 1.5 minutes
	.35 — 4 “	.05 — 1.5 “
	.41 — 4 “	.10 — 3 “
	.46 — Adrenalin, 0.001 mg. per k.	.15 — 2 “
	.47 — 2.5 minutes	.20 — 4 “
	.50 — 3.0 “	.26 — 4.5 “
	.55 — 3.5 “	.31 — 5 “

From 10.47, immediately after the second injection, till 11.20, the average time for clotting was 2.5 minutes, whereas both before and after this period the time

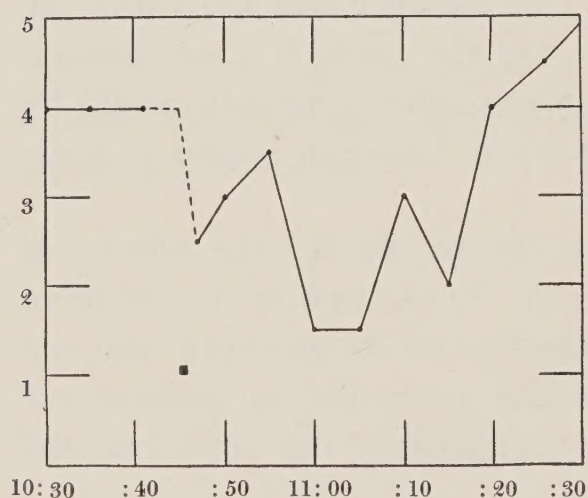


FIGURE 1. Shortening of coagulation time after injecting adrenalin, 0.2 c.c. 1:100,000 (0.001 mg. per k.), at 10.46.

and after this period the time was 4 minutes or longer. At 11.00 o'clock and 11.05, when the end point was reached in 1.5 minutes (a reduction of 63 per cent), a thick jelly was found on examining the cannula. The changes in clotting time in this case are represented graphically in Figure 1.

In another case a dose of 0.0005 mg. per kilo failed to produce any change, but 0.001 mg. per kilo (0.28 c.c. adrenalin 1:100,000, to a cat weighting 2.8 kg.) brought a sharp decline in the record, as follows:

Jan. 9.	11.32 — 6 minutes	11.55 — 4 minutes
	.40 — 6 “	12.00 — 5.5 “
	.47 — Adrenalin, 0.001 mg. per k.	.06 — 7 “
	.48 — 5.5 minutes	

In these instances the animals were decerebrated. For decerebrate cats, the least amount of adrenalin, intravenously, needed to produce shortening of coagulation time is approximately 0.001 mg. per kilo.

In the above cases rapid clotting was manifest directly after minute doses. Larger doses, however, may produce primarily not faster clotting but slower, and that may be followed in turn by a much shorter coagulation time. The figures below present such an instance:

Nov. 25.	2.36 — 3	minutes		3.03 — 1.5	minutes
	.40 — 3	"		.05 — 1.5	"
	.43 —	Adrenalin, 0.5 c.c., 1: 10,000		.07 — 2.5	"
	.44 — 4	minutes		.10 — 1.5	"
	.49 — 3.5	"		.14 — 1.5	"
	.53 — 1.5	"		.16 — 2.5	"
	.55 — 1.5	"		.19 — 3	"
	.58 — 2	"		.23 — 3	"
	3.00 — 2.5	"		.30 — 3	"

This unexpected primary increase of coagulation time, lasting at least six minutes, is in striking contrast to the later remarkable shortening of the process from 3 to an average of 1.7 minutes for more than 20 minutes (see Figure 2, A).

If a strong solution, i.e., 1:10,000, is injected rapidly, the process may be prolonged as above, but not followed as above by shortening, thus:

Nov. 28.	9.59 — 3	minutes		10.18 — 3.5	minutes
	10.03 — 3	"		.22 — 3.5	"
	.08 —	Adrenalin, 0.5 c.c., 1: 10,000		.26 — 3	"
	.10 — 3	minutes		.29 — 3	"
	.14 — 3.5	"		.33 — 3	"

There was in this case no decrease in coagulation time at any test for a half-hour after the injection but instead a lengthening (see Figure 2, B). Howell has reported the interesting observation that repeated massive doses of adrenalin given to dogs may so

greatly retard coagulation that the animals may be said to be haemophilic.¹ These two instances show that on coagulation large doses have the contrary effect to small, just as has been shown to be true for intestinal and arterial smooth muscle.²

In a few experiments the brain and the cord to midthorax were destroyed through the orbit. Artificial respiration then maintained the animal in uniform condition. Under these circumstances, adrenalin intravenously had more lasting effects than when given to the usual decerebrate animals with intact cord. Figure 3 illustrates such a case. For 30 minutes before injection the clotting time averaged 5.4 minutes. Then, about 10 minutes after 1 c.c.

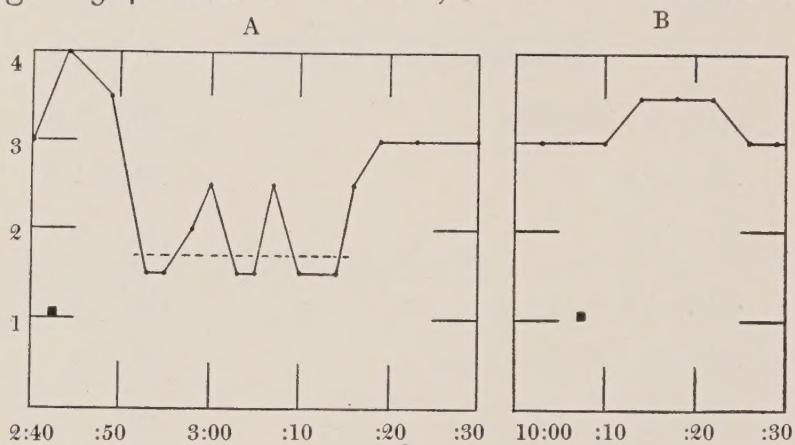


FIGURE 2. *A*, Primary lengthening followed by shortening of the coagulation time when adrenalin, 0.5 c.c. 1:10,000 (0.05 mg.), was injected slowly, at 2.43. *B*, Lengthening of the coagulation time without shortening when the same dose was injected rapidly, at 10.08.

adrenalin 1:50,000 had been slowly injected, clotting began to quicken; during the next 20 minutes the average was 3.4 minutes, and during the following 45 minutes the average was 1.9 minutes — only 35 per cent as long as it had been before the injection.

In another case in which the brain and upper cord were similarly destroyed, the clotting time which for a half-hour had averaged 3.9 minutes was straightway reduced by 1 c.c. 1:100,000 to average for the next hour and 40 minutes 2.3 minutes, with 1.5 and 3 minutes as extremes. During the first 40 minutes of this period of 1 hour and 40 minutes of rapid clotting all of eight tests except two showed a coagulation time of 2 minutes or less.

¹ HOWELL: This journal, 1914, xxxiii, p. xiv.

² HOSKINS: This journal, 1912, xxix, p. 365. CANNON and LYMAN: This journal, 1913, xxxi, p. 376.

The explanation of this persistent rapid clotting in animals with spinal cord pithed is not yet clear.

As indicated in Figures 1, 2 and 3, the records of coagulation show oscillations. Some of these ups and downs are, of course, within the limits of error of the method, but in our experience they have occurred so characteristically after injection of adrenalin, and so often have appeared in a rough rhythm, that they have given the impression of being real accompaniments of faster clotting. It may be that two factors are operating, one tending to

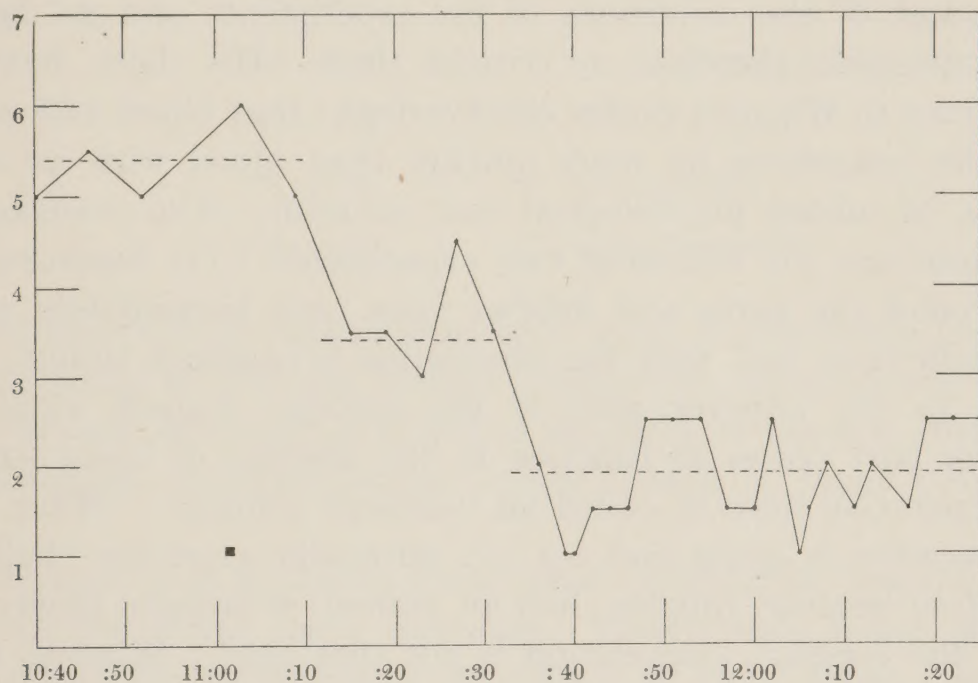


FIGURE 3. Prolonged shortening of the coagulation time after injecting (in an animal with brain and upper cord pithed) adrenalin 1 c.c. 1:50,000 (0.02 mg.) at 11.01-02. The dash-lines represent averages.

hasten, the other to retard the process, and that the equilibrium disturbed by adrenalin is recovered only after interaction to and fro between the two factors.

The oscillations in coagulation time after adrenalin injections suggest that it might vary with changes in blood pressure, for that also commonly oscillates after a dose of adrenalin. Simultaneous recording of blood pressure and determining of coagulation time have revealed that each may vary without noteworthy variation in the other. Within ordinary limits, therefore, changes of blood pressure do not change the rate of clotting.

As previously stated, von den Velden has contended that the shortening of coagulation time by adrenalin is due to exudation of

tissue juices resulting from vasoconstriction. The least amount of adrenalin which produces markedly faster clotting in the cat, however, is 0.001 mg. per kilo. It has been shown that this amount when injected slowly, as in the present experiments, results in brief vasodilation rather than vasoconstriction.¹ Von den Velden's explanation can therefore not be applied to these experiments.

He has claimed, furthermore, that adrenalin added to blood *in vitro* makes it clot more rapidly, but, as already noted, he gives no account of the conditions of his experiments and no figures. It is impossible, therefore, to criticise them. His claim, however, is contrary to Wigger's earlier observations² that blood with added adrenalin coagulates no more quickly than blood with an equal amount of added physiological salt solution. Also contrary to this claim are the following two experiments. (1) Ligatures are tied around the aorta and inferior vena cava immediately above the diaphragm, and thus the circulation is confined almost completely to the anterior part of the animal. Indeed, since the posterior part ceases to function in the absence of blood supply, the preparation may be called an "anterior animal." When such a preparation is made and 0.5 c.c. adrenalin 1:100,000 (half the usual dose because, roughly, half an animal) is injected slowly into one of the jugulars, coagulation is not shortened. Whereas for a half-hour before the injection the clotting time averaged 4.6 minutes, for an hour thereafter the average was 5.3 minutes — a prolongation which may have been due, not to any influence of adrenalin, but to failure of the blood to circulate through the intestines and liver.³ In another experiment after the gastrointestinal canal and liver had been removed from the animal, the average time for coagulation during 25 minutes before injecting adrenalin (0.23 c.c. 1:100,000 in an animal weighing originally 2.3 kg.) was 5.5 minutes; and during 40 minutes after the injection it was 6.8 minutes, with no case shorter than 6 minutes. In the absence of circulation through the abdominal viscera,

¹ CANNON and LYMAN: *loc. cit.*, p. 381.

² WIGGERS: *loc. cit.*, p. 152.

³ See PAWLOW: *Archiv für Physiologie*, 1887, p. 458. BOHR: *Centralblatt für Physiologie*, 1888, ii, p. 263. MEEK: *This journal*, 1912, xxx, p. 173.

therefore, adrenalin fails to shorten the clotting time. (2) The cannulas are filled with adrenalin, 1:1000, and emptied just before being introduced into the artery. The small amount of adrenalin left on the walls is thus automatically mixed with the drawn blood. Alternate observations with these cannulas wet by adrenalin and with the usual dry cannulas show no noteworthy distinction:

Feb. 19.	2.21 — 6.0 minutes,	with usual cannula		
	.30 — 6.5	“	“	“
	.36 — 6.5	“	“	adrenalin cannula
	.49 — 6.0	“	“	“
	.56 — 7.0	“	“	usual cannula
	3.04 — 6.0	“	“	adrenalin cannula

The results of these experiments have made it impossible for us to concede either of von den Velden's claims, i.e., that clotting occurs faster because adrenalin is added to the blood or because adrenalin, by producing vasoconstriction, causes tissues to exude coagulant juices.

Vosburgh and Richards found that coagulation became more rapid as the blood sugar increased. Conceivably faster clotting might result from this higher percentage of blood sugar. Against this assumption, however, is the fact that clotting is greatly accelerated by 0.001 mg. per kilo, much less than the dose necessary to increase the sugar content of the blood.¹ And furthermore, when dextrose (3 c.c. of a 10 per cent solution) is added to the blood of an anterior animal, making the blood sugar roughly 0.3 per cent, the coagulation time is not markedly reduced. Adrenalin appears to act, therefore, in some other way than by increasing blood sugar.

Since adrenalin makes the blood clot much faster than normally in the intact animal, and fails to have this effect when the circulation is confined to the anterior animal, inference is justified that in the small doses here employed adrenalin produces its remarkable effects, not directly on the blood itself, nor through change

¹ CANNON: This journal, 1914, xxxiii, p. 396.

in the extensive neuromuscular, bony, or surface tissues of the body, but through some organ in the abdomen.

That exclusion of the liver from the bodily economy by ligation of its vessels or by phosphorus poisoning,¹ will result in great lengthening of the coagulation time has been clearly shown. The liver, therefore, seems to furnish continuously to the blood a factor in the clotting process which is being continuously destroyed in the body. It is not unlikely that adrenalin makes the blood clot more rapidly by stimulating the liver to discharge this factor in greater abundance. But proof for this suggestion has not yet been established.

SUMMARY

Adrenalin injected in small doses intravenously (0.001 mg. per kilo) and in larger doses subcutaneously, will shorten coagulation time to one-half or one-third the former duration.

The prompt shortening of the process after small doses is changed after larger doses (about 0.03 mg. per kilo) to a lengthening and later a shortening, or to a lengthening alone.

The effect of adrenalin on the clotting time is not associated with any corresponding effect on arterial pressure.

If the blood is confined anterior to the diaphragm, or if the intestines and liver are removed, adrenalin in small doses does not cause rapid clotting.

The addition of small amounts of adrenalin to drawn blood does not hasten clotting.

Increase of dextrose in the blood to 0.3 or 0.4 per cent does not cause the rapid clotting seen after adrenalin injection.

The explanation is suggested that adrenalin accelerates the clotting process by stimulating the liver (and intestines?) to greater activity in discharging some factor or factors in coagulation.

¹ See MEEK: *loc. cit.*, p. 170. Also WHIPPLE and HURWITZ: *Journal of experimental medicine*, 1911, xiii, p. 136.

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